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(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB_4) antagonist is disclosed.

ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. provisional application No. 60/164,902 filed November 11, 1999; the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to a method of treating cancer with radiation therapy. More specifically, it relates to the use of radiation therapy, in conjunction with leukotriene inhibitors which enhance the effectiveness of the radiation therapy.

BACKGROUND OF THE INVENTION

Leukotriene B4 (LTB_4) is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, and shock.

U.S. Patent 5,543,428 discloses the role of leukotriene inhibitors and reversing multi-drug resistance in multi-drug resistant tumors. U.S. Patent 5,910,505 discloses that leukotriene (LTB_4) antagonists may be used for the treatment or inhibition of oral squamous cell carcinoma.

These leukotriene inhibitors are well known in the art, and are fully described in U.S. Patent 5,462,954, which is hereby specifically incorporated by reference for its disclosure of leukotriene inhibitors, the methods of preparation of specific leukotriene inhibitors, and compounds or formulations of the leukotriene inhibitors which may be administered to patients.

Radiation therapy is commonly used to treat cancers such as prostate cancer and colon cancer. Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma, e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Non Small Cell Lung Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, Pediatric Malignancies and the like.
Several types of radiation are used in the treatment of cancer including X-rays gamma rays, high energy electrons and high LET (Linear Energy Transfer) radiation, such as, protons, neutron, and alpha particles. The ionizing radiation is employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons can be produced by linear accelerators and high LET radiation is also applied from radioactive sources implanted interstitially. The total dose of radiation employed by one skilled in the art ranges from 18 to 160 Gray (Gy). (One Gray unit of measure is equal to 100 rads) This total dose of radiation is usually or frequently divided into 5 to 7 continuous weeks of therapy. Typically, one week of radiation is divided into 5 daily fractions. A daily fraction of radiation consists of a dose from 1.2 to 2.5 Gray. The total amount of radiation used in brachytherapy may be 160 Gy. The exact dosage of radiation is dependent on a variety of factors including but not limited to the volume of the cancerous tissue to be irradiated, normal tissue surrounding the cancerous tissue, age of the patient, medical history of the patient, and other clinical factors. Two relevant references are: R. Arriagada,

Hematology/Oncology Clinics of North America, Vol. 11, pgs. 461-472 (1997) and S. Hellman, Principles of Cancer Management: Radiation Therapy, *in* Cancer: Principles and Practice of Oncology, 5th Ed., Lippincott Publishers, pgs. 307-332 (1997); the disclosure of which is herein incorporated by reference.

Whatever the type of radiation used, it is believed that all radiation act against cancer by a similar mechanism. Cancer cells are dividing rapidly, and it is thought that radiation disrupts the DNA of the cancer cells. This creates problems with cell division, and eventually results in the death of the irradiated cancer cells. Radiation also affects the normal tissue, and can lead to the death of normal cells as well. Accordingly, it is highly desirable to minimize the dose of ionizing (electromagnetic) radiation, to which the patient is exposed, in order to provide a treatment which is effective against cancer cells, and at the same time does not cause excessive damage to normal tissues. The need to protect healthy tissues from the effects of radiation, especially high dose radiation, often limits its effectiveness.

Oxygen can act as a potentiator of radiation. Many tumors have rather low levels of oxygen in the interior of the tumor. Often radiation is more effective if oxygen can be provided to the tumor cell. Other potentiators are hypoxic cell sensitizers, non-hypoxic cell sensitizers, and oxygen delivery agents. These potentiators produce enhancement ratios between 1 and 3. Certain oxygen delivery agents are taught in US patent 5,295,944. Advances have been made in understanding the etiology of cancerous cells, and in developing mono or combination therapies for the management and treatment of cancer, with significantly

positive results. Nonetheless, cancer remains one of the major causes of death and the need to find better and more effective therapies is continuously attenuated by factors such as increasing populations, medically advances in other areas that increase life expectancy, and cost.

SUMMARY OF THE INVENTION

The present invention provides a method of treating a human patient suffering from cancer which comprises administering to said patient ionizing radiation in combination with an effective amount of a leukotriene (LTB_4) inhibitor.

Leukotriene (LTB_4) antagonists, particularly, substituted phenylphenol leukotriene (LTB_4) antagonists enhance the effectiveness of radiation therapy in the treatment of cancer.

The present invention is also directed to the use of a leukotriene (LTB_4) antagonist for the manufacture of a medicament for administration to a human patient in combination with ionizing radiation for the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein the term "therapeutically effective amount" is a quantity of leukotriene (LTB_4) inhibitor and/or radiation sufficient to ameliorate the effect of cancer over a period of time either after a single dose, multiple doses, or courses of therapy.

As used herein the term "therapeutically effective interval" is a period of time beginning when one of either the leukotriene (LTB_4) inhibitor or the radiation therapy is

administered or practiced on the patient in need thereof, and ending at the limit of the therapeutic effectiveness of either, or both. Typically, the anti-cancer agents and the leukotriene (LTB_4) antagonist are administered within 24 hours of each other, more preferably within 4 hours and most preferably within 1 hour.

As used herein the terms "parenteral" and "parenteral administration" are synonymous and mean administration of a leukotriene (LTB_4) inhibitor composition by a route such as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, transdermal, transmucosal, transbuccal, transrectal, transvaginal, transnasal or intravenous.

As used herein the terms "Active compound," and "Active ingredient" are synonymous and mean one or more leukotriene (LTB_4) inhibitors useful in the method of the invention.

As used herein the terms "leukotriene (LTB_4) inhibitor," "leukotriene (LTB_4) antagonist," "leukotriene (LTB_4) receptor antagonist," "leukotriene LTB_4 inhibitor," "leukotriene B_4 antagonist," and "leukotriene antagonist" are synonymous.

As used herein the terms "unit dosage" or "dosage unit" mean a prepackaged formulation (i.e., tablets, IV solution and bag, and suppositories) of leukotriene (LTB_4) antagonist compound in discrete therapeutically effective amounts, or a discrete therapeutically effective amount of radiation given in conjunction with leukotriene (LTB_4) antagonist compound formulation.

Surprisingly, we have now found a method of treating a human patient suffering from cancer which comprises administering to said patient ionizing radiation in conjunction (combination) with an effective amount of a leukotriene (LTB_4) inhibitor.

Beneficial effects to cancer patients in the form of improved efficacy, ability to tailor radiation to the receptivity (i.e., ability of patient to undergo radiation based on an aggregate of clinical manifestations) of the patient while treating and/or managing the cancer with leukotriene (LTB_4) antagonists provides a synergistically positive effect for the patient. Similarly, where the patient is less tolerant of leukotriene (LTB_4) antagonists, the combination of leukotriene (LTB_4) antagonists and radiation therapy allows the competent caregiver to tailor the dose of leukotriene (LTB_4) antagonist accordingly, while providing treatment or management of the cancer using radiation therapy concurrently.

Leukotriene B_4 receptor antagonists suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are as follows:
calcitriol, ontazolast, Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, LeoDenmark ETH-615, Ono ONO-4057, Terumo TMK-688, Boehringer Ingleheim BI-RM-270, Ono ONO LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, SmithKline Beecham SB-209247, Searle SC-53228, Sumitomo SM 15178, American Home Products WAY 121006, Bayer Bay-o-8276, Warner Lambert CI-987, Warner Lambert CI-987BPC-15, MacroNex MNX-160, Merck and Co. MK-591, Merck and Co. MK-886, Ono ONO-LB-448, Purdue Frederick PF-5901, Roche Ro 25-3562, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer RP66364, Rhone-Poulenc Rorer RP69698, Shionogi S-2474, Searle SC-50605, Searle SC-41930, Searle SC-50505, Searle SC-51146, Searle SC-52798, SmithKline Beecham SK&F-104493, Leo Denmark SR-2566, Tanabe T-757, and Teijin TEI-1338, Lilly LY213024, Lilly LY264086, Lilly LY255283, Lilly LY210073, Lilly LY247833, and Lilly LY282201, 2-[3-[3-(4-

acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441).

Certain of the above listed leukotriene B_4 receptor antagonists suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are further defined by their chemical names and/or chemical abstract service (CAS) numbers as follow:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441);

b) Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3);

c) Parke-Davis CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5);

d) Pfizer CP-195543 (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl)benzoic acid; CAS Registry Number 204981-48-6);

e) Wyeth-Ayerst WAY-121006 (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3);

f) Bayer Bay-x-1005 ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy)benzeneacetic acid; CAS Registry Number 128253-31-6);

g) Ciba-Geigy CGS-25019C (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)benzamide; moxilubant; CAS Registry Number 147398-01-4);

h) Nattermann & Cie GmbH ebselen (3 2-phenyl-1,2-benzisoselenazol-3(2H)-one; CAS Registry Number 60940-34;

i) LeoDenmark ETH-615 (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]benzoic acid; CAS Registry Number 133430-69-0);

j) Ono ONO-4057 (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropanoic acid; CAS Registry Number 134578-96-4);

k) Terumo TMK-688 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid; CAS Registry Number 110501-66-1);

l) Boehringer Ingleheim BIRM-270 ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast; CAS Registry Number 147432-77-7)

m) Ono ONO-LB457 (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropanoic acid; CAS Registry Number 134578-96-4);

n) Pfizer 105696 (1-[(3S,4R0)-3-([1,1'-biphenyl]-4-ylmethyl)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]Cyclopentanecarboxylic acid; CAS Registry Number 158081-99-3);

o) Perdue Frederick PF 10042 (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]pyrroline; CAS Registry Number 135893-33-3);

p) Rhone-Poulenc Rorer RP 66153 (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid; CAS Registry Number 142422-795);

q) SmithKline Beecham SB-201146 ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid; CAS Registry Number 180208-37-1);

r) SmithKline Beecham SB-201993 ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic acid; CAS Registry Number 150399-22-7);

s) SmithKline Beecham SB-209247 ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant; CAS Registry Number 154413-61-3);

t) Searle SC-53228 (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 153633-01-3);

u) Sumitomo SM 15178 (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl]pyrrolidine; CAS Registry Number 104227-11-4);

v) Bayer Bay 0-8276 (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide; BAY 08276 CAS Registry Number 85259-71-8);

w) Warner Lambert CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5)

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9);

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5);

z) Merck and Co. MK-886 (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7);

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6);

bb) Purdue Frederick PF-5901 (α-pentyl-3-(2-quinolinylmethoxy)benzenemethanol; CAS Registry Number 101910-24-1);

cc) Roche Ro 25-3562 (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane; AI 3-70356; Roller's synthetic juvenile hormone; CAS Registry Number 38896-81-0);

dd) Rhone-Poulenc Rorer RG 14893 (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid; CAS Registry Number 141835-49-6);

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5);

ff) Rhone-Poulenc Rorer RP69698 (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine; CAS Registry Number 141748-00-7);

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3);

hh) Searle SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 138828-39-4);

ii) Searle SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 120072-59-5);

jj) Searle SC-50505 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry 138828-39-4);

kk) Searle SC-51146 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 141059-52-1);

ll) Searle SC-52798 (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 152246-97-4);

mm) SmithKline Beecham SK&F-104493 (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole; CAS Registry Number 111908-95-3);

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5);

oo) Tanabe T-757 (CAS Registry 187112-56-7);

pp) Teijin TEI-1338 [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino]-Benzoic acid methyl ester; CAS Registry Number 119261-58-4);

qq) Lilly LY213024 (5-(3-carboxybenzoyl)-2-)decyloxy)-benzenepropanoic acid; CAS Registry Number 117423-95-7);

rr) LY264086 (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid; CAS Registry Number 135199-82-5);

ss) LY255283 (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone; CGS 23356; CAS Registry Number 117690-79-6);

tt) LY247833 (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol);

uu) LY282201 (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid); and

vv) LY210073 (CAS Registry Number 186912-79-8), and applicable pharmaceutically acceptable salts, stereo or regio isomers thereof.

The salt derivatives of the leukotriene (LTB_4) antagonist used in the composition and method of the invention are pharmaceutically acceptable salts, that include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid (e.g.,

carboxylic acid, sulfonic acid, phosphonic acid) in solution with a base or by exposing the acid to an acidic cation charged ion exchange resin. For example, a carboxylic acidic group (a preferred acidic group) may form a salt by reaction with appropriate bases (e.g., NaOH, KOH) or sodium or potassium charged acidic ion exchange resins to yield the corresponding sodium and potassium salt.

Certain compounds of the compositions or methods of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis and trans isomeric forms of the compounds. The R and S isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis and trans isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are

pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds used in the composition and method of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the acid salt, i.e., sodium salt, of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the acid salt, i.e., sodium salt, of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) with 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

The cancers which may be treated using the present method, are those which are amenable to radiation therapy. These include Breast Carcinoma, Bladder Carcinoma,

Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Non-Small Cell Lung Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Non Small Cell Lung Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, Pediatric Malignancies and the like.

The types of radiation which may be used to treat cancer according to the present invention, are X-rays, gamma radiation, high energy electrons and High LET (Linear Energy Transfer) radiation, such as, protons, neutrons, and alpha particles. The ionizing radiation is employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons can be produced by linear accelerators and high LET radiation is also applied from radioactive sources implanted interstitially. The total dose of radiation employed by one skilled in the art ranges from 18 to 300 Gray (Gy). (One Gray unit of measure is equal to 100 rads) This total dose of radiation is divided into 1 to 7 continuous weeks of therapy. Typically, one week of radiation is divided into 5 daily fractions. The total amount of radiation used in brachytherapy may be 160 Gy. The exact dosage of radiation is dependent on a variety of factors including but not limited to the volume of the cancerous tissue to be irradiated, normal tissue surrounding the cancerous tissue, age of the patient, medical history of the patient, and other clinical factors. Relevant references are: R. Arriagada, Hematology/Oncology Clinics of North America, Vol. 11, pgs. 461-472 (1997) and S. Hellman, Principles of Cancer Management: Radiation Therapy, *in* Cancer: Principles and Practice of Oncology, 5th Ed.,

Lippincott Publishers, pgs. 307-332 (1997); the disclosure of which is herein incorporated by reference.

Preferred Embodiments of the Invention

This invention is a method of treating cancer by administering to a human patient in need thereof a therapeutically effective amount of (a) a leukotriene (LTB_4) antagonist, and a therapeutically effective amount of (b) ionizing radiation; wherein (a) and (b) are both administered within a therapeutically effective interval. The administration of (a) or (b) to a cancer patient may be either continuous or intermittent. However, the treatment plan necessarily involves administration of both (a) and (b) by a dosage regimen or course(s) of treatment deemed advantageous to the patient by the treating physician(s) or specialist.

A. Method of the Invention using simultaneous delivery of leukotriene (LTB_4) inhibitor, and ionizing radiation the leukotriene (LTB_4) inhibitor and ionizing radiation can be delivered simultaneously. A method of simultaneous delivery of the leukotriene (LTB_4) antagonists and an ionizing radiation is to deliver them to the patient separately but simultaneously. Thus, for example, the leukotriene (LTB_4) antagonists may be given as an oral formulation at the same time or within 5 to 60 minutes of the ionizing radiation being administered.

The length of the leukotriene (LTB_4) antagonists' administration can extend past the length of radiation treatment administration.

B. Method of the invention using non-simultaneous delivery of leukotriene (LTB_4) antagonist compound and ionizing radiation.

Each of the essential ingredients, viz., a therapeutically effective amount of (a) leukotriene (LTB_4) antagonists and a therapeutically effective amount of (b) ionizing radiation have a therapeutically effective interval, namely the interval of time in which each agent provides benefit for the patient being treated for cancer. The method of the invention may be practiced by separately dosing the cancer patient in any order with a therapeutically effective amount of (a) leukotriene (LTB_4) antagonists, and a therapeutically effective amount of (b) ionizing radiation provided that each agent is given within the period of time that that the other agent is therapeutically effective against the cancerous cells or tumor.

Typically, intravenous forms of leukotriene (LTB_4) antagonists are therapeutically effective immediately upon administration and up to 5 days later, and preferably in the time interval from 5 minutes after administration to 72 hours after administration. Typically, oral forms of leukotriene (LTB_4) antagonists are therapeutically effective from about 10 minutes to 5 days, and preferably from one-half hour to 72 hours after administration.

Dosage delivery of the leukotriene (LTB_4) antagonists can begin up to 48 hours prior to the ionizing radiation, with the preferred time being up to 24 hours and the most preferred being up to 12 hours prior to the administration of ionizing radiation. Alternatively, dosage of an leukotriene (LTB_4) antagonists can begin up to 48 hours after the initiation of the ionizing radiation therapy with the preferred time being up to 24 hours after and the most preferred being up to 12 hours after.

The leukotriene (LTB_4) antagonist can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal injectable solution. The leukotriene (LTB_4) antagonists are preferably administered parenterally to a cancer patient to insure effective delivery into the bloodstream as fast as possible.

The ionizing radiation may be generated by X-ray produced by instruments such as linear accelerators, or gamma rays produced by radioactive isotope decay. Delivery of ionizing radiation may be by external beam therapy or by brachytherapy. The ionizing radiation may be high energy or low energy depending on factors such as the tissue affected, spread, proximity to tissues or organs less receptive to radiation therapy, patient clinical status (i.e. T cell count and/or other clinical parameters). In general the radiation therapy may be delivered in fractional doses of about 180cGy to about 300 cGy per day for one to five days for 1 to 7 weeks per course of radiation therapy (see Harrison's Principles of Internal Medicine, thirteenth ed., 1994,pages 1826-1830, by McGraw-Hill, Inc., ISBN 0-07-032370-4). This is typically followed by a period of observation by the physician or caregiver, and tissue rebuilding by the patient. The time between courses of radiation therapy, when to initiate radiation therapy in combination with leukotriene (LTB_4) antagonists and when to discontinue are determined by treating authority (physicians, oncologists, and/or radiologists) as appropriate.

The leukotriene (LTB_4) antagonist may be administered during the course of radiation. However, it is preferred that the leukotriene (LTB_4) antagonists be administered for some time before radiation is begun. Such administration allows for an effective level of the leukotriene (LTB_4)

antagonist to be established in the tissue before radiation therapy is undertaken. It is also preferred to begin the administration of the leukotriene (LTB_4) antagonists 1-3 days before the beginning of the radiation therapy, and continue it throughout the course of the radiation therapy or until the cancer is effectively treated, in remission, or a decision to terminate treatment is made. If leukotriene (LTB_4) antagonists are administered after radiation, they should be administered within a therapeutically effective interval.

Preparation of Leukotriene (LTB_4) Antagonist Compounds of the Invention

Leukotriene (LTB_4) antagonist compounds of the invention and their methods of preparation are known to one of skill in the art. These methods are disclosed in issued patent applications and in the non-patent literature. For example, U.S. Patent 5,552,441 and U.S. Patent 5,910,505 both incorporated by herein by reference, disclose methods of preparing certain leukotriene (LTB_4) antagonist compounds. Preparative methods for leukotriene (LTB_4) antagonist compounds of the invention further defined by the CAS registry numbers may be obtained from the literature by cross reference to the CAS registry numbers.

Pharmaceutical Compositions of the Invention

Pharmaceutical compositions useful for the practice of the present invention necessarily denote compositions of the leukotriene (LTB_4) antagonist compound(s) since the accompanying radiation treatment cannot be delivered other than by methods of delivery discussed above. Preferably, leukotriene (LTB_4) antagonist compounds of the invention or pharmaceutical formulations containing same, are in unit

dosage form for administration to a cancer patient. The unit dosage form can be a capsule, an IV bag, a tablet, or a vial. The quantity of Active Ingredient in a unit dose of composition is a therapeutically effective amount and may be varied according to the particular treatment plan and/or amount of accompanying radiation involved. It should be appreciated that it may be necessary to make routine variations to the dosage of leukotriene (LTB_4) antagonist and/or radiation depending on the age and condition of the patient. The dosage of leukotriene (LTB_4) antagonist will also depend on the route of administration.

The leukotriene (LTB_4) antagonist compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the leukotriene (LTB_4) antagonists useful for the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compounds of the invention (e.g., Merck and Co. MK-886 (1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7) together with a pharmaceutically acceptable carrier or diluent therefor. The pharmaceutical formulations of leukotriene (LTB_4) antagonists are prepared by known procedures using well known and readily available ingredients.

In making the leukotriene (LTB_4) antagonist compositions of the present invention, the Active Ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilzed solid or paste, semi-solid, or

liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The leukotriene (LTB_4) antagonist compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of about 0.05 to about 5.0 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution.

Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active Ingredient. In tablets the Active Ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Advantageously, compositions containing the leukotriene (LTB_4) compound, (e.g., Merck and Co. MK-886 (1-[(4-

Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7) may be provided in unit dosage form, preferably each dosage unit or unit dosage containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of Active Ingredient may be administered although it will, of course, readily be understood that the amount of the leukotriene (LTB_4) antagonist compound or compounds actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

Powders and tablets preferably contain from about 1 to about 99 weight percent of the Active Ingredient which is the leukotriene (LTB_4) antagonist compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations of the leukotriene (LTB_4) antagonist compound(s) include suspensions, emulsions, syrups and elixirs.

The Active Ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The Active Ingredient can also be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active Ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 to 3 are illustrative only and are not intended to limit the scope of the invention in any way. "Active Ingredient", refers to a leukotriene (LTB_4) antagonist compound (e.g., (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; CAS Registry Number 118414-82-7) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In one embodiment the compositions of the present invention are combinations of therapeutically effective amounts of the leukotriene (LTB_4) antagonists, noted above, including for example, Merck and Co. MK-886 (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-Indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7) delivered in combination with radiation therapy as discussed previously. The leukotriene (LTB_4) antagonist composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and maybe formulated as sustained release dosage forms and the like.

The method of treating a human cancer patient according to the present invention includes the administration of leukotriene (LTB_4) antagonist and radiation therapy. The leukotriene (LTB_4) antagonist(s) is formulated into

formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of the leukotriene (LTB_4) antagonist. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the leukotriene (LTB_4) antagonist actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations of the leukotriene (LTB_4) antagonists for the combined administration with radiation treatment according to the invention, will normally consist of at least one leukotriene (LTB_4) listed above, mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a

disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the leukotriene (LTB_4) antagonists of this invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially preferred are formulations for oral ingestion.

The following formulation examples may employ as active compounds any of the leukotriene (LTB_4) antagonists noted above. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

FORMULATION EXAMPLE 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
((1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid;; CAS Registry Number 118414-82-7)	250
Starch	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

FORMULATION EXAMPLE 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
((1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; CAS Registry Number 118414-82-7)	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION EXAMPLE 3

Tablets each containing 60 mg of active ingredient are made up as follows:

(1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-Indole-2-propanoic acid; CAS Registry Number 118414-82-7)	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve (355 μm) and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve (1.4 mm). The granules so produced are dried at 50-60° and passed through a No. 18 mesh U.S. sieve (1.00 mm). The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh

U.S. sieve (250 μm), are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg. The following formulation examples illustrate the types of formulations of the leukatriene (LTB_4) antagonists which may be employed in a method of the present invention. The examples may employ as active ingredients any of the leukotriene (LTB_4) antagonist compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

We Claim:

1. A method of treating a human patient suffering from cancer which comprises administering to said patient ionizing radiation in conjunction with an effective amount of a leukotriene LTB_4 inhibitor.

2. A method according to Claim 1 wherein the leukotriene (LTB_4) inhibitor is selected from the group consisting of :

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441);

b) Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3);

c) Parke-Davis CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5);

d) Pfizer CP-195543 (2-[(3S,4R)-3,4-Dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl)benzoic acid; CAS Registry Number 204981-48-6);

e) Wyeth-Ayerst WAY-121006 (2-Fluoro-4'-(2-quinolinylmethoxy)-[1,2'biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3);

f) Bayer Bay-x-1005 ((R)- α-Cyclopentyl-4-(2-quinolinylmethoxy)benzeneacetic acid; CAS Registry Number 128253-31-6);

g) Ciba-Geigy CGS-25019C (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)benzamide; moxilubant; CAS Registry Number 147398-01-4);

h) Nattermann & Cie GmbH ebselen (3 2-phenyl-1,2-benzisoselenazol-3(2H)-one; CAS Registry Number 60940-34);

i) LeoDenmark ETH-615 (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]benzoic acid; CAS Registry Number 133430-69-0);

j) Ono ONO-4057 (2-(4-Carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropanoic acid; CAS Registry Number 134578-96-4);

k) Terumo TMK-688 4-[5-[[2-[4-(Diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid; CAS Registry Number 110501-66-1);

l) Boehringer Ingleheim BIRM-270 ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast; CAS Registry Number 147432-77-7);

m) Ono ONO-LB457 (ONO 4057; (E)-2-(4-Carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]-benzenepropanoic acid; CAS Registry Number 134578-96-4);

n) Pfizer 105696 (1-[(3S,4R0)-3-([1,1'-Biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]cyclopentanecarboxylic acid; CAS Registry Number 158081-99-3);

o) Perdue Frederick PF 10042 (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]pyrroline; CAS Registry Number 135893-33-3);

p) Rhone-Poulenc Rorer RP 66153 (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid; CAS Registry Number 142422-795);

q) SmithKline Beecham SB-201146 ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid; CAS Registry Number 180208-37-1);

r) SmithKline Beecham SB-201993 ((E)-3-[[[[6-(2-Carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic acid; CAS Registry Number 150399-22-7);

s) SmithKline Beecham SB-209247 ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant; CAS Registry Number 154413-61-3);

t) Searle SC-53228 (7-[3-(2-Cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)-propoxy]3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 153633-01-3);

u) Sumitamo SM 15178 (1-[4,11-Dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl]-pyrrolidine; CAS Registry Number 104227-11-4);

v) Bayer Bay 0-8276 (4-Chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide; BAY 08276 CAS Registry Number 85259-71-8);

w) Warner Lambert CI-987 (5-[[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5);

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9);

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5);

z) Merck and Co. MK-886 (1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7);

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6);

bb) Purdue Frederick PF-5901 (α-Pentyl-3-(2-quinolinylmethoxy)benzenemethanol; CAS Registry Number 101910-24-1);

cc) Roche Ro 25-3562 (3-[5-(4-Chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane; AI 3-70356; Roller's synthetic juvenile hormone; CAS Registry Number 38896-81-0);

dd) Rhone-Poulenc Rorer RG 14893 (4-[2-[Methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-Naphthalenecarboxylic acid; CAS Registry Number 141835-49-6);

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5);

ff) Rhone-Poulenc Rorer RP69698 (2-[[5-Methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl-pyridine; CAS Registry Number 141748-00-7)

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3);

hh) Searle SC-50605 (7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 138828-39-4);

ii) Searle SC-41930 (7-[3-(4-Acetyl-3-methoxy-2-propylphenoxy)propoxy]3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 120072-59-5);

jj) Searle SC-50505 (7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry 138828-39-4);

kk) Searle SC-51146 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-Benzopyran-2-propanoic acid; CAS Registry Number 141059-52-1);

ll) Searle SC-52798 (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 152246-97-4);

mm) SmithKline Beecham SK&F-104493 (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-Pyrrolo[1,2-a]imidazole; CAS Registry Number 111908-95-3);

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5);

oo) Tanabe T-757 (CAS Registry 187112-56-7);

pp) Teijin TEI-1338 [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino]benzoic acid methyl ester; CAS Registry Number 119261-58-4);

qq) Lilly LY213024 (5-(3-carboxybenzoyl)-2-)decyloxy)-Benzenepropanoic acid; CAS Registry Number 117423-95-7);

rr) LY264086 (7-Carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid; CAS Registry Number 135199-82-5);

ss) LY255283 (1-[5-Ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]-Ethanone; CGS 23356; CAS Registry Number 117690-79-6);

tt) LY247833 (2-Ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol);

uu) LY282201 (3,4-Dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid); and

vv) LY210073 (CAS Registry Number 186912-79-8), and applicable pharmaceutically acceptable salts, regio and stereoisomers thereof.

3. A method according to Claim 1 wherein the leukotriene (LTB_4) inhibitor is

Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3),

Parke-Davis CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-Thiazolidinedione; CAS Registry Number 127378-46-5),

Pfizer CP-195543 (2-[(3S,4R)-3,4-Dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl)benzoic acid; CAS Registry Number 204981-48-6), or

Wyeth-Ayerst WAY-121006 (2-Fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3).

4. A method according to Claim 1 for the treatment of cancer selected from the group consisting of Prostate Cancer, Colon Cancer, Non-Small Cell Lung Cancer, Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, and Pediatric Malignancies.

5. A method according to Claim 1 wherein the cancer treated is breast cancer, colon cancer, prostate cancer, non-small cell lung cancer, gynecologic carcinoma, pancreatic cancer or testicular cancer.

6. A method according to claim 1 wherein the radiation therapy is administered in fractional doses.

7. A method according to Claim 6 wherein the fractional dose of radiation is from about 160 to 300 cGy.

8. A method according to Claim 1 wherein the dose of leukotriene (LTB_4) inhibitor is from about 5 to 500 mg per day.

9. A method according to Claim 1 wherein the dose of leukotriene (LTB_4) inhibitor is from about 200 to 300 mg per day.

10. A method according to the method of Claim 1 wherein the leukotriene (LTB_4) inhibitor is administered simultaneously, or sequentially.

11. A method according to Claim 1 wherein the ionizing radiation is obtained from particle beam therapy, X-ray, or gamma rays, and delivered by external beam radiation therapy or brachytherapy.

12. Use of a leukotriene (LTB_4) antagonist for the manufacture of a medicament for administration to a human patient in combination with ionizing radiation for the treatment of cancer.

13. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 wherein the ionizing radiation is obtained from particle beam therapy, X-ray, or gamma rays, and delivered by external beam radiation therapy or brachytherapy.

14. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 wherein the leukotriene (LTB_4) inhibitor is selected from the group consisting of:

a) 2-[3-[3-(4-Acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441);

b) Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3);

c) Parke-Davis CI-987 (5-[[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5);

d) Pfizer CP-195543 (2-[(3S,4R)-3,4-Dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl)benzoic acid; CAS Registry Number 204981-48-6);

e) Wyeth-Ayerst WAY-121006 (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3);

f) Bayer Bay-x-1005 ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy)benzeneacetic acid; CAS Registry Number 128253-31-6);

g) Ciba-Geigy CGS-25019C (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)benzamide; moxilubant; CAS Registry Number 147398-01-4);

h) Nattermann & Cie GmbH ebselen (3 2-phenyl-1,2-Benzisoselenazol-3(2H)-one; CAS Registry Number 60940-34);

i) LeoDenmark ETH-615 (4-[[[(3-Fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl]benzoic acid; CAS Registry Number 133430-69-0);

j) Ono ONO-4057 (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropanoic acid; CAS Registry Number 134578-96-4);

k) Terumo TMK-688 4-[5-[[2-[4-(Diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid; CAS Registry Number 110501-66-1);

l) Boehringer Ingleheim BIRM-270 ((S)-N-[2-Cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast; CAS Registry Number 147432-77-7);

m) Ono ONO-LB457 (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropanoic acid; CAS Registry Number 134578-96-4);

n) Pfizer 105696 (1-[(3S,4R0)-3-([1,1'-biphenyl]-4-ylmethy)-3,4-Dihydro-4-hydroxy-2H-1-benzopyran-7-yl]cyclopentanecarboxylic acid; CAS Registry Number 158081-99-3);

o) Perdue Frederick PF 10042 (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]pyrroline; CAS Registry Number 135893-33-3);

p) Rhone-Poulenc Rorer RP 66153 (α,α-Dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid; CAS Registry Number 142422-795);

q) SmithKline Beecham SB-201146 ((E)-3-[6-[[(3-Aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid; CAS Registry Number 180208-37-1);

r) SmithKline Beecham SB-201993 ((E)-3-[[[6-(2-Carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic acid; CAS Registry Number 150399-22-7);

s) SmithKline Beecham SB-209247 ((E)-3-[6-[[2,6-Dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant; CAS Registry Number 154413-61-3);

t) Searle SC-53228 (7-[3-(2-Cyclopropylmethyl)-3-methoxy-4-

[(methylamino)carbonyl]phenoxy)propoxy]3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 153633-01-3);

u) Sumitamo SM 15178 (1-[4,11-Dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl]-pyrrolidine; CAS Registry Number 104227-11-4);

v) Bayer Bay 0-8276 (4-Chloro-N-1H-1,2,4-triazol-3-yl)benzenesulfenamide; BAY 08276 CAS Registry Number 85259-71-8);

w) Warner Lambert CI-987 (5-[[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5);

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9);

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5);

z) Merck and Co. MK-886 (1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methylethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7);

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) Purdue Frederick PF-5901 (α-Pentyl-3-(2-quinolinylmethoxy)-benzenemethanol; CAS Registry Number 101910-24-1);

cc) Roche Ro 25-3562 (3-[5-(4-Chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane; AI 3-70356; Roller's synthetic juvenile hormone; CAS Registry Number 38896-81-0);

dd) Rhone-Poulenc Rorer RG 14893 (4-[2-[Methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid; CAS Registry Number 141835-49-6);

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5);

ff) Rhone-Poulenc Rorer RP69698 (2-[[5-Methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine; CAS Registry Number 141748-00-7)

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3);

hh) Searle SC-50605 (7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 138828-39-4);

ii) Searle SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 120072-59-5);

jj) Searle SC-50505 (7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry 138828-39-4);

kk) Searle SC-51146 (7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 141059-52-1);

ll) Searle SC-52798 (7-[3-[4-(Aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 152246-97-4);

mm) SmithKline Beecham SK&F-104493 (6,7-Dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole; CAS Registry Number 111908-95-3);

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5);

oo) Tanabe T-757 (CAS Registry 187112-56-7);

pp) Teijin TEI-1338 [1R-[1α,2βS(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino]benzoic acid methyl ester; CAS Registry Number 119261-58-4);

qq) Lilly LY213024 (5-(3-carboxybenzoyl)-2-)decyloxy)-benzenepropanoic acid; CAS Registry Number 117423-95-7);

rr) LY264086 (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid; CAS Registry Number 135199-82-5);

ss) LY255283 (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]-Ethanone; CGS 23356; CAS Registry Number 117690-79-6);

tt) LY247833 (2-ethoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol);

uu) LY282201 (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid); and

vv) LY210073 (CAS Registry Number 186912-79-8), and applicable pharmaceutically acceptable salts, regio and stereoisomers thereof.

15. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 wherein the leukotriene (LTB_4) inhibitor is the compound Merck and Co. MK-886 (1-[(4-Chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]- α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7).

16. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 for the treatment of cancer selected from the group consisting of Prostate Cancer, Colon Cancer, Breast Carcinoma, Bladder Carcinoma, Colorectal

Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, and Pediatric Malignancies.

17. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 wherein the cancer treated is breast cancer, colon cancer, gynecologic carcinoma, prostate cancer, non-small cell lung cancer, pancreatic cancer or testicular cancer.

18. Use of a leukotriene (LTB_4) inhibitor according to claim 12 wherein the radiation therapy is administered in fractional doses.

19. Use of a leukotriene (LTB_4) inhibitor according to claim 12 wherein the fractional dose of radiation is from about 160 to 300 cGy.

20. Use of a leukotriene (LTB_4) inhibitor according to the method of Claim 12 wherein the leukotriene (LTB_4) inhibitor is administered simultaneously, or non-simultaneously.

21. Use of a leukotriene (LTB_4) inhibitor according to Claim 12 wherein the ionizing radiation is obtained from particle beam therapy, X-ray, or gamma rays, and delivered by external beam radiation therapy or brachytherapy.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB_4) antagonist is disclosed.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 00/30982

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56387 A (MORRIS DAVID LAWSON ;UNISEARCH LTD (AU)) 17 December 1998 (1998-12-17) page 17, line 30 -page 18, line 2; claims	1-21
P,X	ANDERSON, K. M. ET AL: "Widespread countervailing genomic responses induced by chemotherapy or radiation as a cause of therapeutic failure" MED. HYPOTHESES (2000), 54(6), 1000-1002 , XP001024591 table 1	1-21

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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2001	17/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/30982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SUNDARAM S ET AL: "The vitamin D3 analog EB 1089 enhances the response of human breast tumor cells to radiation." RADIATION RESEARCH, (1999 NOV) 152 (5) 479-86. , XP001024589 abstract; figures	1-21
P,X	SUNDARAM S ET AL: "The vitamin D3 analog EB 1089 enhances the antiproliferative and apoptoti effects of adriamycin in MCF-7 breast tumor cells." BREAST CANCER RESEARCH AND TREATMENT, (2000 SEP) 63 (1) 1-10. , XP001024588 abstract	1-21
X	LAMSON D.W. ET AL: "Antioxidants in cancer therapy;their actions and interactions with oncologic therapies." ALTERNATIVE MEDICINE REVIEW, (1999) 4/5 (304-329). , XP001024599 page 320, column 2	1-21
X	RAMAKRISHNAN, NARAYANI ET AL: "Ebselen inhibition of apoptosis by reduction of peroxides" BIOCHEM. PHARMACOL. (1996), 51(11), 1443-1451 , XP001024541 abstract	1-21
X	REYES A A ET AL: "Role of the 5-lipooxygenase pathway in obstructive nephropathy." KIDNEY INTERNATIONAL, (1992 JAN) 41 (1) 100-6. , XP001024678 abstract; figure 1; table 1	1-21

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-21 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the examples and claims 2-3, 14-15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ..ional Application No
PCT/US 00/30982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9856387 A	17-12-1998	AU 735676 B2	12-07-2001
		AU 7631698 A	30-12-1998
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		CN 1261800 T	02-08-2000
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